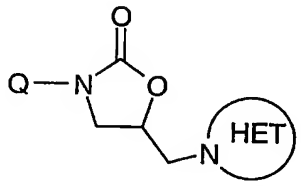
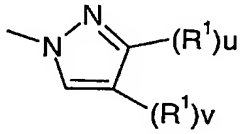
Claims

1. A compound of the formula (I), or a pharmaceutically-acceptable salt, or an in-vivo-hydrolysable ester thereof,

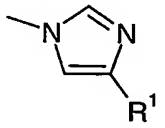


(I)

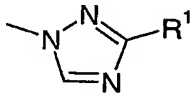
wherein -N-HET is selected from the structures (Ia) to (If) below :-



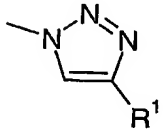
(Ia)



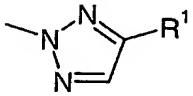
(Ib)



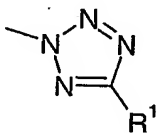
(Ic)



(Id)



(Ie)



(If)

wherein u and v are independently 0 or 1;

R^1 is (1-4C)alkyl;

or R^1 is selected from a substituent from the group

(R^1a) wherein R^1 is halogen, hydroxy, (1-4C)alkoxy, (2-4C)alkenyloxy, (2-4C)alkenyl, (2-4C)alkynyl (optionally substituted on the terminal carbon by CH_2=CH-, di(1-4C)alkylamino, AR2, AR2a or AR2b, wherein AR2, AR2a and AR2b are defined hereinbelow), (3-6C)cycloalkyl, (3-6C)cycloalkenyl, amino, (1-4C)alkylamino, di-(1-4C)alkylamino, (2-4C)alkenylamino, (1-4C)alkyl-S(O)q- (wherein q is 0, 1 or 2), (1-4C)alkylcarbonylamino, ;

or R^1 is selected from the group

(R^1b) wherein R^1 is a (1-4C)alkyl group which is substituted by one substituent selected

from hydroxy, halo, (1-4C)alkoxy, amino, (1-4C)alkylamino, di(1-4C)alkylamino, cyano, azido, (2-4C)alkenyloxy, (1-4C)alkyl-S(O)q- (wherein q is 0, 1 or 2), AR1-S(O)q- (wherein q is 0, 1 or 2 and AR1 is defined hereinbelow), AR2-S(O)q- (wherein q is 0, 1 or 2), AR2a-S(O)q- (wherein q is 0, 1 or 2), benzyl-S(O)q- (wherein q is 0, 1 or 2), (3-6C)cycloalkyl, (3-6C)cycloalkenyl, (1-4C)alkyl-OCO-NH-, (1-4C)alkyl-NHCO-O-, (1-4C)alkylaminocarbonyl, di(1-4C)alkylaminocarbonyl, $H_2NC(=NH)S$-;

or R^1 is selected from a group of formula (R^1c1) :-

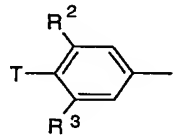
(R^1c1) a fully saturated 4-membered monocyclic ring containing 1 or 2 heteroatoms independently selected from O, N and S (optionally oxidised), and linked via a ring nitrogen or carbon atom; or

or R^1 is selected from the group

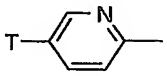
(R^1d) cyano, nitro, azido, formyl, (1-4C)alkylcarbonyl, (1-4C)alkoxycarbonyl, $H_2NC(O)$-, (1-4C)alkylNHC(O)-;

and wherein at each occurrence of an R^1 substituent containing an alkyl, alkenyl, alkynyl, cycloalkyl or cycloalkenyl moiety in (R^1a), (R^1b) or (R^1c1) each such moiety is optionally further substituted on an available carbon atom with one, two, three or more substituents independently selected from F, Cl Br, OH and CN;

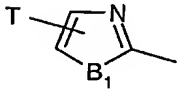
Q is selected from Q1 to Q6 :-



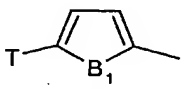
Q1



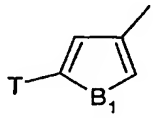
Q2



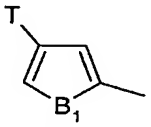
Q3



Q4



Q5

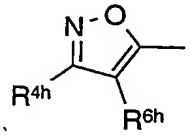


Q6

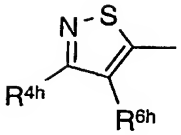
R_2 and R_3 are independently selected from H, F, Cl, CF_3, OMe, SMe, Me and Et;

wherein B_1 is O or S;

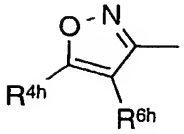
wherein T is selected from the groups in (TAa1) to (TAa12):



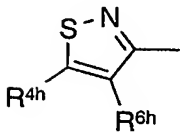
(TAa1)



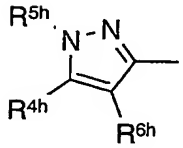
(TAa2)



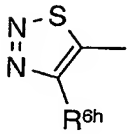
(TAa3)



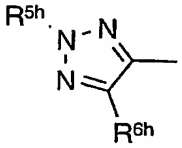
(TAa4)



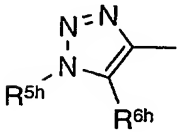
(TAa5)



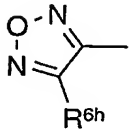
(TAa6)



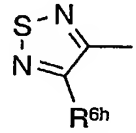
(TAa7)



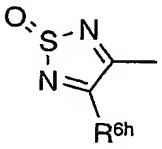
(TAa8)



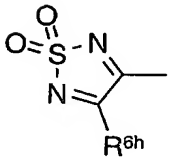
(TAa9)



(TAa10)



(TAa11)



(TAa12)

wherein :

R^{6h} is selected from hydrogen, (1-4C)alkyl, (1-4C)alkoxycarbonyl, (1-4C)alkanoyl, carbamoyl and cyano;

R^{4h} and R^{5h} are independently selected from hydrogen, halo, trifluoromethyl, cyano, nitro, (1-4C)alkoxy, (1-4C)alkylS(O)q- (q is 0, 1 or 2), (1-4C)alkanoyl, (1-4C)alkoxycarbonyl, benzyloxy-(1-4C)alkyl, (2-4C)alkanoylamino, -CONRcRv and -NRcRv wherein any (1-4C)alkyl group contained in the preceding values for R^{4h} and R^{5h} is optionally substituted by up to three substituents independently selected from hydroxy (not on C1 of an alkoxy group, and excluding geminal disubstitution), oxo, trifluoromethyl, cyano, nitro, (1-4C)alkoxy, (2-4C)alkanoyloxy, hydroxyimino, (1-4C)alkoxyimino, (1-4C)alkylS(O)q- (q is 0, 1 or 2), (1-4C)alkylSO2-NRv-, (1-4C)alkoxycarbonyl, -CONRcRv, and -NRcRv (not on C1 of an

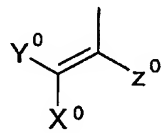
alkoxy group, and excluding geminal disubstitution); wherein Rv is hydrogen or (1-4C)alkyl and Rc is as hereinafter defined;

R^{4h} and R^{5h} may further be independently selected from (1-4C)alkyl {optionally substituted by one, two or three substituents independently selected from hydroxy (excluding geminal disubstitution), oxo, trifluoromethyl, cyano, nitro, (1-4C)alkoxy, (2-4C)alkanoyloxy, phosphoryl [-O-P(O)$(OH)_2$, and mono- and di-(1-4C)alkoxy derivatives thereof], phosphiryl [-O-P$(OH)_2$ and mono- and di-(1-4C)alkoxy derivatives thereof], hydroxyimino, (1-4C)alkoxyimino, (1-4C)alkylS(O)$_q$- (q is 0, 1 or 2), (1-4C)alkylSO_2-NRv-, (1-4C)alkoxycarbonyl, -CONRcRv, -NRcRv (excluding geminal disubstitution), ORc, and phenyl (optionally substituted by one, two or three substituents independently selected from (1-4C)alkyl, (1-4C)alkoxy and halo)}; wherein Rv is hydrogen or (1-4C)alkyl and Rc is as hereinafter defined; and wherein

any (1-4C)alkyl group contained in the immediately preceding optional substituents (when R^{4h} and R^{5h} are independently (1-4C)alkyl) is itself optionally substituted by up to three substituents independently selected from hydroxy (not on C1 of an alkoxy group, and excluding geminal disubstitution), oxo, trifluoromethyl, cyano, nitro, (1-4C)alkoxy, (2-4C)alkanoyloxy, hydroxyimino, (1-4C)alkoxyimino, (1-4C)alkylS(O)$_q$- (q is 0, 1 or 2), (1-4C)alkylSO_2-NRv-, (1-4C)alkoxycarbonyl, -CONRcRv, and -NRcRv (not on C1 of an alkoxy group, and excluding geminal disubstitution); wherein Rv is hydrogen or (1-4C)alkyl and Rc is as hereinafter defined;

or R^{4h} is selected from one of the groups in (TAaa) to (TAab) below, or (where appropriate) one of R^{4h} and R^{5h} is selected from the above list of R^{4h} and R^{5h} values, and the other is selected from one of the groups in (TAaa) to (TAab) below :-

(TAaa) a group of the formula (TAaa1)



(TAaa1)

wherein Z^0 is hydrogen or (1-4C)alkyl;

X^0 and Y^0 are independently selected from hydrogen, (1-4C)alkyl, (1-4C)alkoxycarbonyl, halo, cyano, nitro, (1-4C)alkylS(O)$_q$- (q is 0, 1 or 2), RvRwNSO_2-, trifluoromethyl,

pentafluoroethyl, (1-4C)alkanoyl and -CONRvRw [wherein Rv is hydrogen or (1-4C)alkyl; Rw is hydrogen or (1-4C)alkyl];

(TAab) an acetylene of the formula -≡-H or -≡-(1-4C)alkyl;

wherein Rc is selected from groups (Rc1) to (Rc2) :-

(Rc1) (1-6C)alkyl {optionally substituted by one or more (1-4C)alkanoyl groups (including geminal disubstitution) and/or optionally monosubstituted by cyano, (1-4C)alkoxy, trifluoromethyl, (1-4C)alkoxycarbonyl, phenyl (optionally substituted as for AR1 defined hereinafter), (1-4C)alkylS(O)$_q$- (q is 0, 1 or 2); or, on any but the first carbon atom of the (1-6C)alkyl chain, optionally substituted by one or more groups (including geminal disubstitution) each independently selected from hydroxy and fluoro, and/or optionally monosubstituted by oxo, -NRvRw [wherein Rv is hydrogen or (1-4C)alkyl; Rw is hydrogen or (1-4C)alkyl], (1-6C)alkanoylamino, (1-4C)alkoxycarbonylamino, N-(1-4C)alkyl-N-(1-6C)alkanoylamino, (1-4C)alkylS(O)$_p$NH- or (1-4C)alkylS(O)$_p$-((1-4C)alkyl)N- (p is 1 or 2)};

(Rc2) $R^{13}CO-$, $R^{13}SO_2-$ or $R^{13}CS-$

wherein R^{13} is selected from (Rc2a) to (Rc2d) :-

(Rc2a) hydrogen, (1-4C)alkoxycarbonyl, trifluoromethyl and -NRvRw [wherein Rv is hydrogen or (1-4C)alkyl; Rw is hydrogen or (1-4C)alkyl];

(Rc2b) (1-10C)alkyl

{optionally substituted by one or more groups (including geminal disubstitution) each independently selected from hydroxy, (1-10C)alkoxy, (1-4C)alkoxy-(1-4C)alkoxy, (1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkoxy, (1-4C)alkanoyl, carboxy, phosphoryl [-O-P(O)(OH)$_2$, and mono- and di-(1-4C)alkoxy derivatives thereof], phosphiryl [-O-P(OH)$_2$ and mono- and di-(1-4C)alkoxy derivatives thereof], and amino; and/or optionally substituted by one group selected from phosphonate [phosphono, -P(O)(OH)$_2$, and mono- and di-(1-4C)alkoxy derivatives thereof], phosphinate [-P(OH)$_2$ and mono- and di-(1-4C)alkoxy derivatives thereof], cyano, halo, trifluoromethyl, (1-4C)alkoxycarbonyl, (1-4C)alkoxy-(1-4C)alkoxycarbonyl, (1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkoxycarbonyl, (1-4C)alkylamino, di((1-4C)alkyl)amino, (1-6C)alkanoylamino, (1-4C)alkoxycarbonylamino, N-(1-4C)alkyl-N-(1-6C)alkanoylamino, (1-4C)alkylaminocarbonyl, di((1-4C)alkyl)aminocarbonyl, (1-4C)alkylS(O)$_p$NH-, (1-4C)alkylS(O)$_p$-((1-4C)alkyl)N-, fluoro(1-4C)alkylS(O)$_p$NH-, fluoro(1-4C)alkylS(O)$_p$((1-4C)alkyl)N-, (1-4C)alkylS(O)$_q$- [the (1-4C)alkyl group of (1-4C)alkylS(O)$_q$- being optionally substituted by one substituent selected from hydroxy, (1-4C)alkoxy, (1-4C)alkanoyl, phosphoryl [-O-P(O)(OH)$_2$, and mono- and di-(1-4C)alkoxy

derivatives thereof], phosphiryl [-O-P(OH)$_2$ and mono- and di-(1-4C)alkoxy derivatives thereof], amino, cyano, halo, trifluoromethyl, (1-4C)alkoxycarbonyl, (1-4C)alkoxy-(1-4C)alkoxycarbonyl, (1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkoxycarbonyl, carboxy, (1-4C)alkylamino, di((1-4C)alkyl)amino, (1-6C)alkanoylamino, (1-4C)alkoxycarbonylamino, N-(1-4C)alkyl-N-(1-6C)alkanoylamino, (1-4C)alkylaminocarbonyl, di((1-4C)alkyl)aminocarbonyl, (1-4C)alkylS(O)$_p$NH-, (1-4C)alkylS(O)$_p$-((1-4C)alkyl)N-, and (1-4C)alkylS(O)$_q$-;

(Rc2c) R^{14}C(O)O(1-6C)alkyl wherein R^{14} is AR1, AR2, (1-4C)alkylamino (the (1-4C)alkyl group being optionally substituted by (1-4C)alkoxycarbonyl or by carboxy), benzyloxy-(1-4C)alkyl or (1-10C)alkyl {optionally substituted as defined for (Rc2b)};

(Rc2d) R^{15}O- wherein R^{15} is benzyl, (1-6C)alkyl {optionally substituted as defined for (Rc2c)} or AR2b;

wherein

AR1 is an optionally substituted phenyl or optionally substituted naphthyl;

AR2 is an optionally substituted 5- or 6-membered, fully unsaturated monocyclic heteroaryl ring containing up to four heteroatoms independently selected from O, N and S (but not containing any O-O, O-S or S-S bonds), and linked via a ring carbon atom, or a ring nitrogen atom if the ring is not thereby quaternised;

AR2a is a partially hydrogenated version of AR2, linked via a ring carbon atom or linked via a ring nitrogen atom if the ring is not thereby quaternised;

AR2b is a fully hydrogenated version of AR2, linked via a ring carbon atom or linked via a ring nitrogen atom.

2. A compound of formula (I) as claimed in Claim 1, or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein Q is Q1.

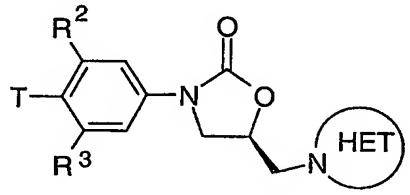
3. A compound of formula (I) as claimed in Claim 1 or Claim 2, or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof,
wherein -N-HET is 1,2,3-triazol-1-yl or tetrazol-2-yl.

4. A compound of formula (I) as claimed in any one of Claims 1 to 3, or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof,
wherein R^2 and R^3 are independently hydrogen or fluoro.

5. A compound of formula (I) as claimed in any one of Claims 1 to 4, or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein T is selected from TAa1, TAa5, TAa7 and TAa8.

6. A compound of formula (I) as claimed in any one of Claims 1 to 5, or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein R^1 is selected from R^1a to R^1d;

7. A compound of formula (I) as claimed in any one of Claims 1 to 6, which is a compound of formula (IB)or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof,



(IB)

wherein -N-HET is 1,2,3-triazol-1-yl or tetrazol-2-yl;
R^1 is (1-4C)alkyl;
R^2 and R^3 are independently hydrogen or fluoro; and
T is selected from TAa1, TAa5, TAa7 and TAa8.

8. A pro-drug of a compound as claimed in any one of the previous claims.

9 A method for producing an antibacterial effect in a warm blooded animal which comprises administering to said animal an effective amount of a compound of the invention as claimed in any one of Claims 1 to 7, or a pharmaceutically-acceptable salt, or pro-drug or in-vivo hydrolysable ester thereof.

10. A compound of the invention as claimed in any one of Claims 1 to 7, or a pharmaceutically-acceptable salt, or pro-drug or in-vivo hydrolysable ester thereof, for use as a medicament.

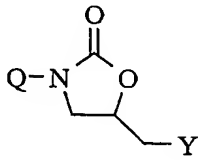
11. The use of a compound of the invention as claimed in any one of Claims 1 to 7, or a pharmaceutically-acceptable salt, or pro-drug or in-vivo hydrolysable ester thereof, in the manufacture of a medicament for use in the production of an antibacterial effect in a warm blooded animal.

12. A pharmaceutical composition which comprises a compound of the invention as claimed in any one of Claims 1 to 7, or a pharmaceutically-acceptable salt or pro-drug or an in-vivo hydrolysable ester thereof, and a pharmaceutically-acceptable diluent or carrier.

13. A process for the preparation of a compound of formula (I) as claimed in Claim 1 or pharmaceutically acceptable salts or pro-drug or in-vivo hydrolysable esters thereof, which process comprises one of processes **(a)** to **(g)**:

(a) by modifying a substituent in, or introducing a new substituent into, the substituent group Q of another compound of formula (I) ; or

(b) by reaction of a compound of formula (II) :



(II)

wherein Y is a displaceable group with a compound of the formula (III) :

-N-HET

(III)

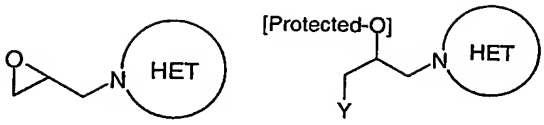
wherein –N-HET (of formula (Ia) to (If), already substituted and optionally protected) is HN-HET (free-base form) or ⁻N-HET anion formed from the free base form; or

(c) by reaction of a compound of the formula (IV) :

Q-Z

(IV)

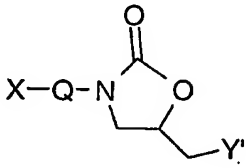
wherein Z is an isocyanate, amine or urethane group with an epoxide of the formula (V) wherein the epoxide group serves as a leaving group at the terminal C-atom and as a protected hydroxy group at the internal C-atom; or with a related compound of formula (VI) where the hydroxy group at the internal C-atom is protected and where the leaving group Y at the terminal C-atom is a leaving group;



(V) (VI)

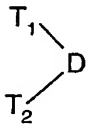
or

(d) (i) by coupling, using catalysis by transition metals, of a compound of formula (VII) :



(VII)

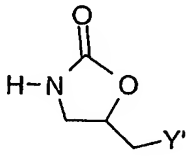
wherein Y' is a group –N-HET as hereinbefore defined, X is a replaceable substituent; with a compound of the formula (VIII), or an analogue thereof, which is suitable to give a T substituent as defined by (TAa1–TAa12) in which the link is via an sp^2 carbon atom (D = CH=C-Lg where Lg is a leaving group; or as in the case of reactions carried out under Heck reaction conditions Lg may also be hydrogen)



(VIII)

where T_1 and T_2 may be the same or different and comprise a precursor to a ring of type T as hereinbefore defined, or T_1 and T_2 may together with D form a ring of type T as hereinbefore defined;

(d) (ii) by coupling, using catalysis by transition metals, of a compound of formula (VIIA):



(VIIA)

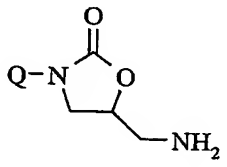
wherein Y' is a group HET as hereinbefore defined, with a compound

[Aryl]-X

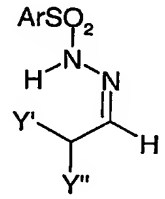
where X is a replaceable substituent;

(e) Where N-HET is 1,2,3-triazole by cycloaddition via the azide (wherein Y in (II) is azide), with a substituted acetylene or masked acetylene;

(f) Where N-HET is 1,2,3-triazole by synthesis with a compound of formula (IX), namely the arenesulfonylhydrazone of acetaldehyde, by reaction of a compound of formula (II) where Y = NH_2 (primary amine);

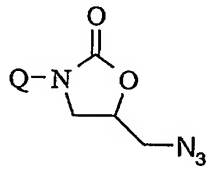


(II : Y = NH2)



(IX)

(g) Where N-HET is 1,2,3-triazole by cycloaddition via the azide (wherein Y in (II) is azide) with acetylene using Cu(I) catalysis in to give the N-1,2,3-triazole;



(II : Y = N_3)

and thereafter if necessary :

i) removing any protecting groups;

ii) forming a pro-drug (for example an in-vivo hydrolysable ester); and/or

iii) forming a pharmaceutically-acceptable salt.